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A COMPARISON OF CORTISONE AND ASPIRIN IN THE TREATMENT OF EARLY CASES OF RHEUMATOID ARTHRITIS

A SECOND REPORT BY THE JOINT COMMITTEE OF THE MEDICAL RESEARCH COUNCIL AND NUFFIELD FOUNDATION ON CLINICAL TRIALS OF CORTISONE, A.C.T.H., AND OTHER THERAPEUTIC MEASURES IN CHRONIC RHEUMATIC DISEASES*

The therapeutic trial here presented was designed to answer, as stated in the first report,† a specific but important question—namely, in early and uncomplicated cases of rheumatoid arthritis is it possible to maintain the patient's well-being more efficiently by treatment with cortisone than by treatment with aspirin? At the same time it was hoped to study the evolution of the rheumatoid process during prolonged therapy with these two different agents. In other words, the aim was to measure the therapeutic effects upon the rheumatoid process of a long-term treatment initiated while that process was still uncomplicated, either by severe anatomical changes in the joints or by metabolic disturbances resulting from a prolonged and debilitating disease.

For this purpose 61 adult patients, regarded as suitable for treatment with *either* agent, were admitted to six centres in England and Scotland. Thirty of these patients were treated with cortisone and 31 with aspirin, their allocation to one or other treatment being made entirely at random (within each centre and for patients of each sex and duration of illness). By such means two comparable groups of these early cases were constructed. Observations of the groups made one week, eight weeks, thirteen weeks, and approximately one year after the start of treatment showed that they had run a closely parallel course in nearly all respects—for example, in joint tenderness, strength of grip, tests of dexterity of hand or foot, clinical assessments of the activity of the disease and of the patient's functional capacity. "For practical purposes, therefore," the first report concluded, "there appears to have been surprisingly little to choose between cortisone and aspirin in the management of these 61 patients in the early stages of rheumatoid arthritis." In the present report the comparison is extended to approximately two years from the beginning of treatment.

Full details of the trial were given in the first report but will be briefly recapitulated here.

The Patients

Each patient included in the trial (*a*) had a polyarthritis of rheumatoid type affecting at least four joints and bilateral involvement of either hands or feet, ankles or wrists; (*b*) had had the disease for not less than three and not more than nine months; and (*c*) was aged between 17 and 59 years. A sheep-cell agglutination test was performed in most of them during the first year of observation (53 of the total 61) and gave a positive result in nearly three-quarters.

The two groups of patients, on cortisone and aspirin respectively, were initially almost identical in the numbers of men and women, in the numbers aged 17–39 and 40–59 years, and in the numbers with a duration of symptoms of three to five or six to nine months. In each of the six centres the cases admitted were almost equally divided between cortisone and aspirin. The initial equalities or inequalities in the characteristics studied will be seen in the tables that follow.

Treatment

For the first year of treatment it was laid down that therapy would be given in twelve-weeks courses separated by one week off treatment. Each course would start with a standard dosage, after which the physician was free to adjust the dose to suit the requirements of individual patients. The specified courses, given in divided doses not fewer than three times a day, were:

		Cortisone	*Aspirin*
First week:	Day 1	300 mg.	6 g.
„ „	„ 2	200 „	6 „
„ „	„ 3 to day 7 ..	100 „ daily ..	6 „ daily
Second week:	„ 8 „ „ 14 ..	50 „ „ ..	2 „ „
Third to twelfth week:	„ 15 „ „ 84 ..	Individualized at 25 to 200 mg. daily with graded withdrawal in week 12	Individualized at 1 to 8 g. daily with graded withdrawal in week 12

In the "free" period—that is, the third to twelfth week—the physician was asked to employ the minimum dosage that would restore maximal functional efficiency without producing serious side-effects. In the thirteenth week no treatment by cortisone or aspirin was given, observations and measurements being made (in this week analgesics other than aspirin could, if necessary, be given). If symptoms recurred the twelve-weeks

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The results of the trial were analysed by Dr. J. T. Boyd, of the Statistical Research Unit of the Medical Research Council, London School of Hygiene and Tropical Medicine, and the subcommittee is greatly indebted to him for his work.

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course was repeated, except that the selected dose for the individual patient replaced the standard dose of the second week.

During the second year these twelve-weeks courses were replaced by continuous treatment—unless the patient was in remission or was thought to require no maintenance dose. The dosage throughout the year was entirely at the physician's discretion, but the aim was again to employ the minimum that would produce maximum functional efficiency and relief of symptoms without producing serious side-effects.

Assessments

The clinical assessment included (*a*) a defined judgment of the patient's general functional capacity (for the five grades laid down, see Table X); (*b*) a judgment of the activity of the disease as inactive, slightly active, or very active; and (*c*) a statement whether the patient appeared to be in remission. In addition to these subjective assessments the clinician was required to measure the strength of grip for each hand. (The patient had to squeeze an oblong rubber bag 5 by 3 in. (12.5 by 7.5 cm.) inflated at a pressure of 10 mm. Hg, and the figure recorded was the average of three grips.) Two tests of dexterity were applied—namely, in patients with affected hands the time taken to tie six double knots with 12-in. (30-cm.) pieces of household string, and in patients with affected legs the time taken to go up and down ten steps. Estimates were also made of joint tenderness and of range of movement. Complications and side-effects were noted. The only obligatory laboratory tests were the blood sedimentation rate and the haemoglobin level.

Towards the end of the second year *x*-ray pictures of the hands and feet were taken and the amount of porosis and erosion revealed in each was assessed.

The Data

During the first year's observation three patients were lost from the trial—all three from the group treated with aspirin, reducing the number in that group to 28. It was concluded in the first report that two of these ought to be regarded as failures of treatment and should be remembered as such in considering the results (a male who deteriorated after some preliminary improvement, and, feeling after six months that he was gaining no benefit, was taken out of the trial and given other treatment; and a female who relapsed on leaving hospital, had a psychological breakdown, and did not attend further. The third patient, who did well on aspirin, went to New Zealand at week 30). No losses took place in the second year, and observations are available for all the 58 patients previously reported. It must be noted, however, that during the second year six patients (one on cortisone and five on aspirin) were known to have received some treatment other than that laid down (there was, however, no transfer from one treatment group to the other). These were:

(*a*) Two patients on aspirin who did not attend regularly in the second year (Postgraduate Medical School Centre).

(*b*) Two patients on aspirin (West London Centre) who had their aspirin therapy discontinued in weeks 55 and 72.

(*c*) One patient on aspirin (Edinburgh Centre) who had severe side-effects and the drug discontinued in week 55.

(*d*) One patient on cortisone (Edinburgh Centre) who had severe side-effects and the hormone discontinued in week 55.

These patients have been retained in their original groups, which are thus composed of 30 patients on cortisone, one of whom was given some other treatment (not aspirin), and 28 patients on aspirin, five of whom were given some other treatment (not hormone).

The treatment schedule laid down for the second year required continuous therapy until the last four weeks (except in cases already in remission or thought not to require any maintenance dose). In weeks 100 to 104 a gradual "tapering off" was called for, followed by four weeks without treatment and an assessment at the end of this period—that is, in week 108. The centres were not, however, able to fulfil this schedule in all cases, and for about one-third of each group no "off-treatment" assessment was made (nine of each treatment group). In some cases the withdrawal of treatment was regarded as unjustifiable, and in others signs of relapse following a reduction of dosage caused the full amount required for maintenance to be restored. On the other hand, assessments were available for all 58 patients at some point close to the end of the year while they were still on their personal dosage. The week chosen for analysis, therefore, was, for each patient, that week of personal dosage which provided assessments and was nearest to week 104—with the proviso that it must lie at least four weeks before an off-treatment week—that is, before any "tapering off" of dosage would have begun. There were six patients (three on cortisone and three on aspirin) who had been off treatment for all or part of the second year; in these cases the personal dosage was taken to be nil and the week nearest to the end of the year was chosen for analysis. The actual points taken lay between the 96th and 112th weeks in all cases.

Results

In the first report the changes under treatment were shown for each group between the start of treatment and the end of the first week, between week 1 and week 8, and between week 8 and one year. It has not been thought necessary to present the intermediate data again, and the tables that follow show the picture at the start of treatment and the end of the first and second years.

(a) Joint Tenderness

In reaching the figures for joint tenderness set out in Table I an overall "tenderness" index was first computed separately for each patient by taking the average of his recorded joints. The mean of these averages gave, at each point of time, an index for the treatment group as a whole. It will be seen that the average position at the start of treatment was almost identical in the two groups—namely,

TABLE I.—*The Average Levels of the Joint Tenderness Index**

Joints Measured	Treatment Group	Average Joint Tenderness		
		Start of Treatment	End of 1 Year	End of 2 Years
All relevant joints (including wrist and hand, given below)	Cortisone	1·91	0·74	0·72
	Aspirin	1·89	0·76	0·58
Wrist-joints	Cortisone	1·80	1·00	0·93
	Aspirin	1·93	0·96	0·73
Small joints of hand ..	Cortisone	2·25	0·58	0·63
	Aspirin	2·05	0·53	0·31

* Tenderness was graded on the scale 0 for no pain, 1 for slight pain, 2 for wincing, and 3 for wincing and withdrawal. The records have been used as an ordinary numerical scale.

TABLE II.—*Joint Tenderness Index (all relevant joints) at the End of Two Years Related to the Initial Levels of Tenderness. Number of Patients*

Joint Tenderness at Start of Treatment	Treatment Group and No. of Patients	Joint Tenderness at End of 2 Years				
		0	Under 1	1–	2–	3
Under 1 ..	Cortisone .. 1		1			
	Aspirin .. 3	1	2			
1– ..	Cortisone .. 13	2	6	4	1	
	Aspirin .. 7	4	3			
2– ..	Cortisone .. 11	3	4	3	1	
	Aspirin .. 13	3	5	4	1	
3 ..	Cortisone .. 5	2	2	1		
	Aspirin .. 5	1	3			1
Total ..	Cortisone .. 30	7	13	8	2	0
	Aspirin .. 28	9	13	4	1	1

1.91 cortisone and 1.89 aspirin—and that the decline in tenderness during the first year was considerable and strikingly similar—to 0.74 cortisone and 0.76 aspirin. During the second year the average for the cortisone group has remained almost the same (0.72), while for the aspirin group the figure has declined further to 0.58. Division of the joints into those of the wrists and of the hand (the main components of the total index) gives a very similar picture in each group—that is, equality at one year and a lower figure in the aspirin group at two years. The differences at two years are not, however, statistically significant, and too much emphasis must not be placed upon them. Table II gives the numbers of patients with different levels of joint tenderness at the start of treatment and at the end of two years. The equality of the two groups is again noticeable. Thus, for the joints recorded at the start of treatment, 7 of the 30 patients on cortisone had no remaining joint tenderness at all at the end of two years, in 13 it was slight, and in 10 it was more definite. The corresponding figures for the 28 observed patients on aspirin were 9, 13, and 6. The numbers available are small, but the same equality of trend is suggested in each subdivision of the table.

(b) Range of Movement and Strength of Grip

Table III gives the figures for range of movement in the wrists and strength of grip. In these respects the cortisone group had, by chance and on the average, some advantage over the aspirin group when treatment was started. At the end of one year both groups had improved considerably. At this point of time the averages of the cortisone group remained above those of the aspirin group, but the advantage was no greater than had been observed at the start of treatment. At the end of two years even that gap has narrowed, both groups having shown a very slight deterioration during the second year and there being no significant difference between them at the end of the second year. The frequency with which various ranges of wrist movement were observed are shown in Table IV, and the changes in strength of grip in Table V. Neither table reveals any clear advantage to one or other treatment.

TABLE III.—*The Average Measurements of (a) Range of Wrist Movement and (b) Strength of Grip*

Characteristic Measured	Treatment Group	Average Measurement		
		Start of Treatment	End of 1 Year	End of 2 Years
Range of wrist movement (in degrees)	Cortisone	99*	120*	111
	Aspirin	78	103	103
Strength of grip (in mm. Hg) left hand	Cortisone	138	202*	187
	Aspirin	111	164	158
Strength of grip (in mm. Hg) right hand	Cortisone	134	187	186
	Aspirin	116	166	164

* The mean of the cortisone group was significantly greater than the mean of the aspirin group.

TABLE IV.—*Range of Movement (wrists) at Two Years Related to the Initial Range of Movement. Number of Wrists Involved*

Range of Movement (Degrees) at Start of Treatment	Treatment Group	Range of Movement at End of 2 Years (Degrees)			
		0–	50–	100–	150+
0–	2 Cortisone		2		
	9 Aspirin		5	3	1
50–	12 Cortisone	1	5	5	1
	13 Aspirin		6	6	1
100–	12 Cortisone		2	6	4
	11 Aspirin		6	4	1
150+	3 Cortisone			1	2
	0 Aspirin				
Total	29 Cortisone	1	9	12	7
	33 Aspirin	0	17	13	3

TABLE V.—*Number of Patients Showing Given Improvement or Deterioration in Their Strength of Grip (in mm. Hg) Between Start of Treatment and End of Two Years*

Treatment Group and No. of Patients	Improved by 100 mm. or More	Improved by up to 100 mm.	No Change	Deteriorated by up to 100 mm.	Deteriorated by 100 mm. or More
Left hand:					
30 Cortisone	7	14	1	6	2
28 Aspirin	4	15	3	6	—
Right hand:					
30 Cortisone	11	12	1	5	1
28 Aspirin	7	14	1	6	—

(c) Tests of Dexterity

Table VI gives the results of the timing tests. The improvement noted at the end of one year has been maintained, but not increased, during the second year of treatment. The two treatment groups remain very similar in these respects.

TABLE VI.—*The Average Time Taken to (a) Tie Six Knots and (b) Go Up and Down Ten Steps by Patients with Affected Hands and Legs Respectively*

Characteristic Measured	Treatment Group	Average Time (in Seconds)		
		Start of Treatment	End of 1 Year	End of 2 Years*
Time to tie 6 knots	Cortisone	38	29	29
	Aspirin	41	34	33
Time to go up and down 10 steps	Cortisone	14	11	11
	Aspirin	18	13	11

* 8 patients (5 cortisone, 3 aspirin) included in the earlier averages had no recording for either dexterity test at two years.

(d) Haemoglobin Level and Blood Sedimentation Rate

During the first year of the trial it was found that the haemoglobin level and blood sedimentation rate responded, on the average, rather more favourably to cortisone than to aspirin. During the second year this advantage to the cortisone group has not been maintained (Table VII). While its average values for the haemoglobin level and erythrocyte sedimentation rates have both remained practically unchanged, the average haemoglobin value in the aspirin group has risen and the average E.S.R. has fallen. As a result the two treatment groups differ little in the average haemoglobin level and negligibly in the average E.S.R. at the end of two years. Looking beneath the averages to individual levels of the E.S.R., the same picture of close similarity is revealed (Table VIII). Taking under 20 mm./hour as the level of normality, 10 of the 30 patients on cortisone and 11 of the 28 on aspirin had a normal E.S.R. at the end of two years of treatment, while 11 and

TABLE VII.—*The Average Levels of (a) Haemoglobin and (b) Blood Sedimentation Rate*

Characteristic Measured	Treatment Group	Average Measurement		
		Start of Treatment	End of 1 Year	End of 2 Years
Haemoglobin (g.%)	Cortisone	12·2	13·1*	13·0
	Aspirin	12·1	11·3	12·3
E.S.R. (mm./hr.)	Cortisone	42	27	29
	Aspirin	42	35	28

* The averages shown by the cortisone and aspirin groups differ significantly.

TABLE VIII.—*Number of Patients With Given Blood Sedimentation Rates at the End of Two Years Related to Their Rates at the Start of Treatment*

E.S.R. (mm./hr.) at Start of Treatment	Treatment Group and No. of Patients	E.S.R. (mm./hr.) at End of 2 Years			
		0–	20–	40–	60+
0–	9 Cortisone	6	3		
	5 Aspirin	3	2		
20–	6 Cortisone	1	3	2	
	11 Aspirin	5	4	2	
40–	9 Cortisone	2	5	1	1
	7 Aspirin	2	5		
60+	6 Cortisone	1		3	2
	5 Aspirin	1	1	2	1
Total ..	30 Cortisone	10	11	6	3
	28 Aspirin	11	12	4	1

12 respectively had an elevated rate (20–39) and nine and five had a considerably elevated rate (40 or over). Within the subgroups with different levels at the start of treatment the trend also appears to have been remarkably similar in the two groups.

(e) Clinical Assessments

At the end of the second year four patients on cortisone and four on aspirin were reported to be in remission. The overall clinical assessments of condition at the end of the first and second years are shown in Table IX.

TABLE IX.—*Clinical Assessment of Activity at End of One Year and End of Two Years*

Grade	End of 1 Year		End of 2 Years	
	Cortisone	Aspirin	Cortisone	Aspirin
Inactive	2	2	4	4
Slightly active ..	21	19	20	19
Very active ..	7	7	6	5
Total ..	30	28	30	28

The assessments of functional capacity are given in Table X, and at the end of two years the two treatment groups still remain, as was noted at one year, more remarkable for their similarity than for their dissimilarity. In each treatment group 21 patients were regarded as capable either of full work (grade 1) or of light work (grade 2), and subdivision of them shows 14 patients in grade 1 in the cortisone group and 13 in the aspirin group. Seven of the 30 patients on cortisone remained seriously incapacitated (grade 3), compared with 5 of the 26 patients on aspirin. Only two patients, both on cortisone, were still grossly incapacitated, and against this may be placed the two aspirin cases who progressed unfavourably in the first year and were lost sight of—that is, putting the most unfavourable complexion upon them.

TABLE X.—*Number of Patients with Given Functional Capacity at Different Stages of the Trial**

Treatment Group	Time of Assessment	Functional Capacity			Total
		1 or 2	3	4 or 5	
Cortisone	Start of treatment	4	18	8	30
Aspirin		5	18	6	29†
Cortisone	End of 1 year	23	5	2	30
Aspirin		21	5	0	26
Cortisone	End of 2 years	21	7	2	30
Aspirin		21	5	0	26

* Functional capacity grades were:
Grade 1: Fully employed or employable in usual work and able to undertake normal physical recreation.
„ 2: Doing light or part-time work and only limited physical recreation. For housewives, all except the heaviest housework.
„ 3: Not employed and unemployable. No physical recreations. Housewives only light housework and limited shopping.
„ 4: Confined to house or wheel-chair, but able to look after themselves in essentials of life. Hospital patients confined to bed.
„ 5: Completely bedridden.

† No record was made in this respect for two patients, and three were lost sight of during the first year of the trial. The two patients not assessed at the start of treatment had functional capacities at the end of two years of 1 and 2 respectively.

(f) X-ray Observations

X-ray films of the hands were taken for all 30 patients on cortisone and for 27 of the 28 patients on aspirin during the second half of the second year of the trial. For the feet, films were available for 26 patients on cortisone and 24 on aspirin. All these films were read independently by three observers (a clinician at one of the centres and two radiologists), who assessed the degree of porosis and erosion present in each case without knowing the treatment group to which it belonged. The results are shown in Tables XI and XII. It is clear that while observers B and C were similar in their interpretations of the films, observer A had a quite different standard—particularly in porosis. For instance, no or doubtful porosis of the hands (grades 0 and 1) was recorded for 20 and 21 patients on cortisone by observers B and C, but for only 14 by observer A. An

TABLE XI.—*X-ray Films of the Hand. Number of Patients with Given Gradings at the End of Two Years by Three Independent Observers*

Grade*	Cortisone			Aspirin		
	Observer			Observer		
	A	B	C	A	B	C
	Porosis					
0	5	16	13	4	10	7
1	9	4	8	6	4	11
2	8	7	7	11	10	8
3	5	2	1	4	3	1
4	3	1	1	2	0	0
Total ..	30	30	30	27	27	27
Average grade	1·73	0·93	0·97	1·78	1·22	1·11
	Erosion					
0	6	7	9	3	5	3
1	5	7	5	3	4	4
2	11	12	12	8	7	16
3	5	3	4	11	10	4
4	3	1	0	2	1	0
Total ..	30	30	30	27	27	27
Average grade	1·80	1·47	1·37	2·22	1·93	1·78

* Gradings of porosis and erosion were: 0=Nil. 1=Doubtful. 2=Slight. 3=Moderate. 4=Severe.

TABLE XII.—*X-ray Films of the Feet. Number of Patients with Given Gradings at the End of Two Years by Three Independent Observers*

Grade	Cortisone			Aspirin		
	Observer			Observer		
	A	B	C	A	B	C
	Porosis					
0	5	18	14	3	14	12
1	8	3	9	6	6	8
2	5	3	1	10	3	2
3	6	1	2	4	1	2
4	2	1	0	1	0	0
Total ..	26	26	26	24	24	24
Average grade	1·69	0·62	0·65	1·75	0·63	0·75
	Erosion					
0	9	7	7	5	6	3
1	4	10	9	0	3	6
2	7	4	9	10	7	12
3	4	4	1	5	8	3
4	2	1	0	4	0	0
Total ..	26	26	26	24	24	24
Average grade	1·46	1·31	1·15	2·13	1·71	1·63

analysis of variance shows these differences between the observers, in their gradings of both porosis and erosion, to be highly significant ($P<0.001$).

Comparison between the treatment groups shows that for each observer the mean figures for porosis and erosion of the hands and feet are rather higher in the aspirin group than in the cortisone group. The differences are very small for porosis but more marked for erosion. The analysis of variance shows that they are not statistically significant. A simple summation of the readings of the three observers gives the following proportions with some degree of porosis or erosion (grades 2, 3, and 4):

	Porosis		*Erosion*	
	Cortisone	*Aspirin*	*Cortisone*	*Aspirin*
Hands ..	39% ..	48% ..	57% ..	73%
Feet ..	27% ..	32% ..	41% ..	68%

The differences are again relatively slight (except, perhaps, for erosion of the feet), and, with the numbers of patients involved, none of them is significant. It is not possible to compare the *changes* that have taken place in these respects in the two treatment groups, since *x*-ray films were not one of the requirements at the start of the trial. *X*-ray films were, however, taken initially in some patients, and it is possible to make use of these. Thus there were 16 patients in the aspirin group and 25 in the cortisone group for whom *x*-ray films of the hands were available at the start of treatment and at the end of two years, and 8 and 11

respectively with *x*-ray films of the feet. The latter are too few to be of any value, and examination suggests also that they may well be an unrepresentative group. On the other hand, the 16 patients on aspirin for whom *x*-ray pictures of the hands were available had at the start of treatment average measurements in joint tenderness, grip, etc., very similar to the total aspirin group. In these respects, therefore, those whose hands were *x*-rayed do not appear to be a biased group. To allow comparison of the recorded changes in porosis and erosion in these 16 patients on aspirin each has been matched with a cortisone patient with the same initial degree of porosis or erosion. (Where more than one appropriate cortisone patient was available a random choice was made.) This comparison of the 16 matched patients shows that at entry to the trial some degree of porosis (slight, moderate, or severe) was recorded as present in 45% of the readings in each treatment group. At the end of two years the percentage was 40 in the cortisone group and 55 in the aspirin group, slight and not significant changes. In erosion the initial percentage was only 6 in each treatment group, but at the end of two years this had increased to 65 in the cortisone group and 74 in the aspirin group. The change here is large, but is similar in both groups. On the basis of these admittedly limited figures for the hands there is clearly no material difference between the progression of the two treatment groups.

(g) Side-effects

During the first year of treatment side-effects were recorded for 19 patients in the cortisone group and 21 in the aspirin group. During the second year the numbers were 19 and 12. Most of these patients had more than one side-effect, the most frequent in the cortisone group being oedema of the ankles (8 cases), moon-face or rubicundity (6), depression (5), euphoria (4), and obesity (3); in the aspirin group the most frequent were nausea, dyspepsia, or anorexia (6), tinnitus (4), and oedema of the ankles (3). In only two cases, one in each treatment group, were these side-effects severe enough to necessitate the discontinuance of treatment. The patient on cortisone, a woman aged 36, suffered from persistent and severe headache, depression, dyspepsia, and vomiting, and had occasional casts of red blood cells in the urine. The patient on aspirin, a man aged 40, had marked dyspepsia and vomiting.

The Maintenance Doses

The maintenance doses that were being employed at the end of the second year are set out in Table XIII. They do not differ appreciably from those in use at the end of the first year, when the average values were 80 mg. of cortisone and 4.5 g. of aspirin.

TABLE XIII.—*Daily Maintenance Doses Being Administered at the End of the Second Year (Before any Tapering Off)*

Cortisone (mg./day)	No. of Patients on Given Dose	Aspirin (g./day)	No. of Patients on Given Dose
125	1	6·7	2
100	6	6	2
75	11		
62½	3	5*	4
50	3	4	9
37½	1	3·3	1
25	1	2·7	1
		2	1
Total	26	Total	20
Mean value	75 mg.	Mean value	4·5 g.
Not receiving cortisone	4	Not receiving aspirin	8

* Including 1 at 5·3.

Discussion

In the first year of this trial of the treatment of early cases of rheumatoid arthritis it was decided that the treatment should be tapered off at the end of each three-months period and then withheld for a week to allow an assessment of the patient's condition. At the end of the first of these courses of treatment it was found that there was distinct "relapse" in some of the patients, though, it is important to note, an equal degree of "relapse" occurred on the two forms of treatment, cortisone and aspirin. Such "relapses," even though minor in degree, were clearly undesirable, and it was therefore decided that treatment should be continuous throughout the second year of the trial (and, indeed, in a number of cases it became continuous before the end of the first year). At the end of this continuous treatment, which allowed a maintenance dose entirely at the physician's discretion, an assessment was made, usually while the patient was on a maintenance dose (or on no dose if in remission). Thus comparisons can now be made between the two groups at approximately the end of two years of treatment (between weeks 96 and 112 from the start of treatment), the second year's treatment having been uninterrupted.

In total, 61 patients were admitted to the trial, 30 being allocated at random to cortisone and 31 to aspirin. Three of the patients in the aspirin group were lost sight of during the first year, of whom two could be regarded as failures of that treatment and one, who migrated, as a success so far as it went. During the second year none has been lost to sight, and measurements and assessments are available for all 58 patients in most respects. On the other hand, it must be noted that the aspirin group contains four patients who had some additional therapy (not hormone) during the second year, while there was also one patient in the aspirin group and one in the cortisone group whose treatment was discontinued as a result of severe side-effects. These few changes are hardly sufficient to disturb materially the comparison of the two groups. It may be added, too, that a separate analysis has been made, for several of the features given in the tables above, for the patients on cortisone and aspirin who were at the three centres where the only changes were the discontinuance of treatment in one cortisone and one aspirin case. Here there could be no bias, and the results were found to parallel closely those set out in full for the total groups. Attention may therefore be confined to these total groups.

The results of the trial continue at the end of two years to show a similarity between the two treatment groups that is almost remarkable. In some respects the average values for the two groups have come even closer together than they were at the end of one year—either by slight improvement in the aspirin group or by a slight falling-off in the cortisone group. This applies to the range of wrist movement, the strength of grip, and the tests of dexterity. In joint tenderness the cortisone group shows no change in its average index, while the aspirin group shows a reduction. None of these differences, however, is statistically significant. At the end of one year, on the other hand, it was shown that the haemoglobin level and blood sedimentation rate had, on the average, responded rather more favourably to cortisone than to aspirin. This advantage of the cortisone group has vanished during the second year. The mean and frequency distribution of the sedimentation rates are almost identical and the mean haemoglobin levels no longer differ significantly.

A new measure has been introduced to the trial by means of *x*-ray films of the hands and feet of the patients, assessed independently and "blindly" by three observers. Their estimates of the degree of porosis and erosion shown by each patient reveal very little difference between the two treatment groups in respect of porosis, but some excess of erosion in the aspirin group. This excess, however, is not more than might fairly easily arise by chance. The relative position of the two groups in this respect at the start of treatment is unknown, since *x*-ray examinations were not demanded at entry. A study of such *x*-ray films of the hands as were available suggests, however, that neither group has changed appreciably in the incidence of porosis. Both groups show a very considerable rise in the recorded incidence of erosion, but differ little from one another.

Clinical assessments of the patient's condition continue to show no difference between the two groups. With almost

equal numbers at risk, four in each group were in remission, six on cortisone and five on aspirin were "very active," 14 on cortisone and 13 on aspirin were regarded as capable of doing their usual work and of taking normal physical recreation, nine on cortisone were still gravely incapacitated and seven on aspirin (including here the two unsuccessful cases lost to sight in the first year). As at the end of one year the two groups retain their equality.

Summary

A further report is made on 61 patients who were allocated at random to treatment with either cortisone (30 cases) or aspirin (31 cases) while they were still in the early stages of rheumatoid arthritis. In their second year of therapy treatment with one or other agent has been continuous, and "individualized" by the physician in charge of the patient to meet each patient's needs. At approximately the end of two years of treatment 58 of the original 61 patients have been reassessed clinically, submitted to some simple objective tests, had *x*-ray films taken of their hands and feet, and had their haemoglobin levels and blood sedimentation rates measured. In no respect do the two groups differ by more than might easily be due to chance, and in most respects they are distinguished more by their equalities than by their differences. At the end of two years, therefore, as previously reported at the end of one year, it appears that for practical purposes there has been remarkably little to choose between cortisone and aspirin in the management of this group of patients.

INTRAMUSCULAR IRON IN INFANCY

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A good doctor will always be chary of using, or recommending, parenteral therapy when oral treatment can lead to equally good results less unpleasantly. Iron has been given by mouth for many years with excellent results, both in the ferric state as iron and ammonium citrate, and more recently as ferrous sulphate, which has been used increasingly since it has been recognized that only in the ferrous state can iron be absorbed and that ferric salts have to be reduced by the acid gastric juice before they can be utilized. Naturally, iron has been used particularly in paediatrics for the treatment of iron-deficiency anaemia—that is, of nutritional origin—and in infants so affected the associated hypochlorhydria can only act as a deterrent to full utilization of ferric salts. In any case, it is well known that only a portion, even of the ferrous salts, is absorbed when given by mouth, and the size of this portion depends on the physiological functioning of the gastro-intestinal secretory and absorptive mechanisms. With ferrous sulphate it is usually considered that not more than 14% utilization can be obtained. A utilization coefficient of 28% is given for ferrous gluconate (Haler, 1952). Although oral iron is usually effective, it has certain disadvantages. It is unpleasant, and may cause vomiting and intestinal upsets. In some cases the parents do not give the prescribed dose, or give it only irregularly, and if it causes any upset they stop further treatment without informing the doctor, and so the desired effect is not achieved. It is probable that the intestinal mucosal barrier prevents the absorption of iron in excess of immediate haemoglobin requirements, so that adequate stores are never accumulated. In addition, it takes some time for the effects of oral iron to be evident clinically, and this time factor is of great importance. Often infants with nutritional anaemia are not seen until the anaemia is well developed, and, as anaemia probably represents a final stage of a general tissue depletion, an affected infant will have been disturbed metabolically for some time previously. He may have been unwell generally, and, when exposed to the hazards of infection, reacted less well than a normal infant. Any increased speed of response to treatment would therefore be most valuable.

Intravenous iron preparations are utilized completely and rapidly. But, as is to be expected from the difficulty of the administration of these substances, they are not often used in practice. Several observers have reported their experiences with small groups of children (Granrud and Øster, 1950; Hanna and Shehata, 1951; Beaujon, 1951; Hagberg, 1951; Schöner, 1952; Stransky and Dauis-Lawas, 1952; Wiesener, 1952). The largest series was that of Dickstein and his colleagues (1952), who treated 80 infants and children, of whom 66 were suffering from nutritional anaemia.

The introduction of an active, efficient, relatively painless intramuscular preparation, free from undesirable side-effects, would be a welcome advance in therapy for infants unable to tolerate or utilize oral iron and for those in whom rapidity of response was important, or in those in whom transfusion was difficult technically and iron might be a fair substitute.

There is, of course, already a British Pharmacopoeial preparation of iron for injection. It is, however, very painful and requires the addition of a local analgesic with every injection.

Present Investigation

This report describes the use of a new product—"imferon"—which is a stable, non-irritant preparation of an iron-dextran complex, containing 50 mg. of elemental iron per ml. Treatment of adults with this preparation has already been described (Baird and Podmore, 1954; Cappell *et al.*, 1954; Scott and Govan, 1954; Jennison and Ellis, 1954), but there have not so far been any reports of its use in infants.

We have treated more than 100 infants and children with this preparation, but we are here reporting only the results with initial groups who have been followed up for some months. The first infants treated were suffering from nutritional anaemia. Included among these were a few infants who had been premature at birth and who presented at 10–12 months of age with the "anaemia of prematurity." They responded so well to treatment that we next treated a group of infants attending the follow-up clinic for premature infants, many of them irregular attenders who, on being rounded up, were found to be anaemic. We then decided to try the effect of the prophylactic use of intramuscular iron in premature infants in the hope of preventing the otherwise almost inevitable anaemia of prematurity from developing later. In addition, there were several other infants who were anaemic as a result of haemorrhage, and these we have grouped as surgical cases.

Results

All haemoglobin values are on the scale 100% = 14.8 g. Sideroblasts were looked for in methanol-fixed films and